REMARKS

Restriction Requirement

Applicants note that Claims 3-8 remain pending while the allowance of a generic claim is evaluated. Applicants note that the Examiner is obligated to examine the generic claims and again submits that the scope of the claims of the present invention is not limited to the elected species.

Defective Declaration

The Examiner contends that the inventors' Declaration is defective. Enclosed herewith is a substitute Declaration which is in compliance with 37 CFR 1.67(a).

Information Disclosure Statement

The Examiner has stated that the Information Disclosure Statement filed October 5, 2001 fails to comply with 37 CFR 1.97 and 1.98 because it lacks copies of the cited references. Applicants' return postcard, which was submitted with the Information Disclosure Statement filed October 5, 2001 and which was returned with acknowledgment by the Patent Office, indicates that the references were included. Applicants are enclosing herewith duplicate copies of the references for the Examiner's convenience. Since the original submission of references was timely and acknowledged by the Patent Office, Applicants do not believe that fees are due in connection with the submission of reference copies. The Examiner's consideration of the references is respectfully requested.

Rejection of Claims 1, 9-11, 18, 19, 23, 25, 27, 28, and 31-35 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1, 9-11, 18, 19, 23, 25, 27, 28, and 31-35 under 35 U.S.C. § 102(b), contending that these claims are anticipated by U.S. Patent No. 5,871,734 to Lobb et al., as evidenced by U.S. Patent No. 5,869,448 to Arrhenius et al. Specifically, the Examiner contends that Lobb et al. teach the use of an antibody against VLA-4 to treat asthma. The Examiner asserts that VLA-4 is a receptor on T cells and that Lobb et al. teach that administration of VLA-4 antibodies results in a 70% decrease in inhibition of late phase response.

Applicants traverse the rejection of Claims 1, 9-11, 18, 19, 23, 25, 27, 28, and 31-35 under 35 U.S.C. § 102(b). Initially, Applicants note that Claim 1 has been amended to clarify, as set forth

in the specification (see page 9, lines 23-26), that the aerosolized antibody used in the claimed method is one which, as a result of contact with the antibody, causes the depletion or inactivation of the T cell. On page 11, lines 19-27, the specification teaches:

> As used herein, a "receptor on a T cell" generally refers to any receptor that is expressed by a T cell (i.e., a T lymphocyte). Such receptors include, but are not limited to, the T cell antigen receptor (also referred to herein as a TCR), including TCRs from both αβ and γδ T cells; the CD3 complex; CD4; and CD8. To be useful in the present invention, the binding of the receptor by an antibody must result in neutralization (depletion, removal) of the T cell. Therefore, preferred receptors to target using the present method are any receptors that, when bound by a depleting (e.g., neutralizing) antibody, cause the depletion or immobilization (e.g., apoptosis via complement activation, blockage, removal, or phagocytosis) of the T cell to which the antibody binds.

In contrast to the present method, the method taught by Lobb et al. uses antibody against VLA-4 to treat asthma. VLA-4 is an *integrin* molecule that is referred to as an *adhesion receptor* by the Arrhenius et al. and that is found on T cells as well as other cells of the hematopoietic system. Integrins are molecules that are involved in cell-cell adhesion and migration of cells and do not play a direct role in T cell activation. It is known in the art the binding of an integrin will not cause depletion or inactivation of T cells. Indeed, Lobb et al. teach that binding of anti-VLA-4 to leukocytes is believed to inhibit the migration of such cells to the lung tissue (*e.g.*, eosinophils and neutrophils), which is completely different than the mechanism by which the present invention operates (i.e., depletion or inactivation of a T cell by binding to a receptor on the T cell that is associated with activation).

Therefore, Lobb et al. do not teach or suggest the presently claimed method, which makes use of an aerosolized antibody that selectively binds to a receptor on a T cell and causes the depletion or inactivation of the T cell. In view of the foregoing amendment and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 9-11, 18, 19, 23, 25, 27, 28, and 31-35 under 35 U.S.C. § 102(b).

Rejection of Claims 1-3 and 9-35 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-3 and 9-35 under 35 U.S.C. § 103, contending that these claims are unpatentable over Lobb et al. as evidenced by Arrhenius et al. in view of Schramm et al. Specifically, the Examiner contends that Lobb et al. teach the use of an antibody against VLA-4, including by aerosol administration, to treat asthma and notes that VLA-4 is a receptor on T cells. The Examiner acknowledges that Lobb et al. do not teach the use of an anti-TCR αβ antibody, but contends that Schramm et al. teach that intravenous administration of αβ TCR can be used to treat asthma. The Examiner contends that it would have been *prima facie* obvious to have created the claimed invention because Lobb et al. and Schramm et al. each teach an antibody that binds to T cells and because Lobb et al. teach a variety of modes of administration of anti-VLA-4, including aerosol administration. The Examiner further asserts that a neutralizing antibody would be used because Schramm et al. teach that asthma symptoms are reduced in the absence of αβ T cells.

Applicants traverse the Examiner's rejection of Claims 1-3 and 9-35 under 35 U.S.C. § 103. Initially, Applicants refer to the discussion above and note that Claim 1 has been amended to clarify that the aerosolized antibody used in the claimed method is one which, as a result of contact with the antibody, causes the depletion or inactivation of the T cell. Applicants submit that the Examiner has failed to produce a *prima facie* case of obviousness in view of the combination of Lobb et al., Arrhenius et al. and Schramm et al.

To establish a *prima facie* case of obviousness, the combination of references cited by the Examiner must: (1) teach each and every element of the claimed invention; (2) provide the requisite motivation to combine the references to arrive at the claimed invention; and (3) provide a reasonable expectation of success to arrive at the claimed invention.

First, the combination of references fails to teach each and every element of the claimed invention because none of the reference teach or suggest the use of an aerosolized antibody that meets the limitations of binding to a receptor on a T cell and causing the depletion or inactivation of the T cell. Lobb et al. teach an aerosolized VLA-4 antibody, but this is not an antibody that causes depletion or inactivation of the T cell. Schramm et al. do not teach an aerosolized antibody.

Second, even if the Examiner argues that one of skill in the art would be motivated to combine the antibody of Schramm et al. with the aerosol delivery of a completely different antibody of Lobb et al., Applicants submit that there is no motivation to combine the references as the

Examiner has done. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggesting supporting the combination. ACS Hospital Systems v. Montofiore Hospital, 221 USPQ 929, 933 (Fed.Cir. 1974). "A statement that modifications of the prior art to meet the claim limitations would have been 'well within the ordinary skill of the art at the time the invention was made', because the cited references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)." MPEP 2143.01.

More specifically, as discussed in detail above, VLA-4 and the claimed T cell receptors are completely different receptors, such that antibodies that bind to the receptors will have completely different effects on the T cell. Lobb et al. specifically teach that binding of anti-VLA-4 to leukocytes (*e.g.*, eosinophils and neutrophils) inhibits the migration of such cells to the lung tissue. VLA-4 binds to a large spectrum of different cells and therefore, anti-VLA-4 would act by changing the migration/distribution of several different cell types, not just T cells. Indeed, Lobb et al. teach that their method operates by inhibiting the migration of leukocytes, and primarily eosinophils and neutrophils, to lung tissue. In contrast, the antibody of the present invention , allows the *removal and/or inactivation* of a small and relevant population of *T cells* which are directly involved in the allergic inflammatory response *in the lung*. Lobb et al. do not teach or suggest providing a different antibody than VLA-4 nor any other mechanism of inhibiting allergic inflammation other than inhibiting the migration of leukocytes to lung tissue and therefore, Lobb et al. can not provide motivation to switch to a different antibody, including the one taught by Schramm et al. and as such, does not provide motivation to make the combination as the Examiner has done. Schramm et al. provides no motivation to combine with Lobb et al., because Schramm et al. specifically teaches the *systemic* use of αβ TCR antibodies by intravenous administration, which is completely different than aerosol administration. Schramm et al. do not teach or suggest using aerosol administration of αβ TCR antibodies. As taught in the specification, prior to the present invention, it was thought that antibodies delivered by aerosol must be administered in high doses to overcome the effects of expected low potency and to successfully reach the target airways (see page 10, lines 22-26). Given this general theory in the art and that the teachings of Schramm et al. are directed to intravenous

administration, there is no motivation provided to switch to a different type of administration, and certainly not to look to Lobb et al. which teaches a completely different antibody that operates via a different mechanism than αβ TCR antibody. Therefore, there is no motivation provided by either reference to make the combination as the Examiner has done.

Third, there is no expectation of success provided by the combination of references at being able to make and use the claimed invention. As will be recognized, claims cannot be found obvious unless the prior art teaches or suggests making the claimed product or process and that there is a reasonable expectation of success at doing so. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir., 1991) (The teaching or suggestion to make the claimed combination or modification and the reasonable expectation of success must both be found in the prior art). Since Lobb et al. teach the use of anti-VLA-4, which operates by inhibiting migration of leukocytes to the lung tissue, this reference can not provide any expectation of success at using an antibody that is directed to a completely different receptor and that operates by a completely different mechanism for the treatment of asthma, just as Lobb et al. can not provide any expectation of success of using any other type of treatment for asthma then the one specifically taught in that patent. Schramm et al. can not provide any expectation of success at using aerosolized administration of an antibody because the reference is not directed to aerosol administration. The combination of references fails to provide an expectation of success because there is no teaching or suggestion of administration of an aerosolized antibody as claimed.

Finally, Applicants submit that the claimed invention provides unexpected and surprising advantages over the prior teachings in the art. First, the claimed method targets pulmonary T cell populations in the absence of any substantial effect on peripheral T cells, which is a large advantage over previously described methods (e.g., the method of Schramm et al.), which target T cell responses systemically, since peripheral immune responses (i.e., immune responses outside the localized area of delivery, such as in the spleen or lymph nodes) are neither substantially stimulated nor substantially inhibited. Systemically administered antibodies target all T cells including developing T cells, whereas the aerosolized antibodies of the present invention primarily target T cells at the effector stage, i.e. functionally differentiated T cells. Second, in contrast reports of the administration of other aerosolized antibodies (e.g., anti-IgE administration, described by Fahy et al. (1999, *Am. J. Respir. Crit. Care Med.* **160**:1023-1027)), the present inventors have demonstrated

that the claimed method is highly effective at reducing airway hyperresponsiveness. Third, the present inventors have provided evidence in the specification that targeting T cells that are present at the allergic site by the localized administration method of the present invention reduces allergic inflammation-associated exacerbation of AHR *without affecting the adaptive immune system.* Finally, and most surprisingly, in contrast to the evidence and assertions generally in the art that antibodies delivered by aerosol must be administered in high doses to overcome the effects of expected low potency and to successfully reach the target airways, the method of the present invention is effective at extremely *low* doses of antibody. Indeed, the method of the present invention achieves efficacy with antibody doses that are believed to be about *1000-fold* or more lower than systemic doses of antibody required to achieve the same effect.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3 and 9-35 under 35 U.S.C. § 103.

Applicants have attempted to address all of the Examiner's concerns as raised in the January 13 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner has any additional questions or concerns regarding Applicants' position, he is encouraged to contact the below-named agent at (303) 863-9700.

Respectfully submitted,

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